DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

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CBER #98-022

AUG 4 1998

Certified-Return Receipt Requested

WARNING LETTER

Barry Miskin, M. D.
Palm Beach Research Center
1897 Palm Beach Lakes Blvd., #120
West Palm Beach, Florida 33409

Dear Dr. Miskin:

During an inspection ending on April 17, 1998, Ms. Angela K. Rhodes, an investigator with the Food and Drug Administration (FDA), met with you to review your conduct of several clinical studies. The inspection is part of FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational drugs.

The following protocols were reviewed by the FDA investigator:

1. A Double-Blind, Randomized, Parallel Group Study to Evaluate [redacted] Treatment Regimens [redacted] subjects enrolled in the study. At least [redacted] subjects were screened.

2. A Double-Blind, Placebo-Controlled, Parallel Group, Randomized Study Evaluating the [redacted] subjects enrolled in the study. [redacted] others signed informed consent.

3. Clinical Protocol for Efficacy and Safety Evaluation of a [redacted] subjects enrolled in the study.

4. Protocol [redacted], A Multicenter, Double-Blind, Phase III, [redacted] There are [redacted] currently active subjects. [redacted] additional subjects were screened.

5. [redacted], A [redacted]-Week Phase II Multi-Center, Randomized, Open-Label Study to [redacted]

There are [redacted] active subjects and [redacted] screen failures.

The Florida District Office provided us with a copy of your letter dated April 29, 1998, in which you responded to the FDA Form 483 (copy enclosed) left with you at the end of the inspection. Although your responses adequately describe your corrective actions for some of the deviations listed on the FDA Form 483, your letter did not address some of the items listed below. For some items below, we have additional comments pertaining to observed conditions or your response to the 483. The deviations described below include reference to the applicable federal regulations published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312]. The deviations include, but are not limited to the following:

1. **Failure to ensure that the investigation is conducted according to the investigational plan (protocol). [21 CFR 312.60]**

   There are several protocol deficiencies regarding collection of specimens, eligibility criteria of subjects, and changes of initial results. For example:

   a. The protocol (study #1 listed above) requires a minimum [redacted] Subject [redacted] entered the study with a [redacted] on 5/29/97 as shown by the [redacted] The [redacted] sheet records [redacted] as the original target [redacted]

      Please explain why the width measurement was changed to [redacted] on the [redacted]

   b. The protocol for study #2 indicates that the investigator will determine the [redacted]. In addition, the sponsor sent a letter to you dated 3/25/97 indicating the need to identify at the onset of the study the type of individual (e.g. M.D., study coordinator, nurse) responsible for assisting with the [redacted]. Prior to interaction with subject [redacted] you indicated in a FAX to the sponsor on 3/26/97 that another physician would perform these functions. A Study Coordinator determined the [redacted] f [redacted] /) at baseline on 7/11/97. The Study Coordinator is a non-physician.

      We note that you delegated authority to the study coordinator for this assessment. Please assure us that this is not a common practice at your site.

c. Subject ——— was randomized to the study even though the ——— did not meet entry criteria. Entry criteria for the ——— is ——— At baseline on 7/11/97 the ———, on 7/15/97 the ——— according to telephone notes, and on 7/18/97 the ——— The sponsor agreed to allow the subject to continue since the subject was already randomized.

Please explain how you will prevent future occurrences. Your response indicates the ——— was particularly difficult to obtain because the subject's condition was extremely ——— Why was the study coordinator sent to make the assessment and ——— on such a difficult case? Did the study coordinator make assessments or ——— for other subjects?

2. **Failure to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR Part 312.60]**

According to copies of documents submitted to the ——— subject ——— signed the informed consent form on 1/13/97, prior to local IRB approval of the protocol. The ——— is responsible for studies at the ——— where the subject signed the consent form. The ——— did not approve study #2 listed above until 2/19/97. Please explain why the informed consent process began prior to IRB approval of the study and how you will prevent similar occurrences in future studies you conduct.

3. **Failure to prepare and maintain adequate case histories designed to record all data observations pertinent to the investigation. [21 CFR 312.62(b)].**

a. Tracings of ——— (study #1) for subjects ——— and ——— for the following dates were not available at the time of inspection:

i. Subject ——— 3/27/97, 4/2/97, 4/10/97, 4/16/97, 4/23/97, 4/30/97, 5/7/97, and 5/21/97.

ii. Subject ——— 4/8/97, 4/15/97, 4/22/97, 4/29/97, 5/6/97, 5/20/97.

We note that the above tracings were submitted with your response. We remind you that the regulations require you to maintain source documents.

b. The case report form and data recorded on a paper towel show the ——— for subject ———) as ———, but the worksheet data show the ——— We remind you that it is not appropriate to collect source data on materials such as paper towels. Please explain how you will prevent future occurrences.

c. There is no documentation in source data for visits on 5/8/97 and 6/25/97 by subject ——————————). Only telephone notes and photos were found regarding the visits. The telephone notes discuss laboratory testing for the subject. Please explain why there is no source documentation to show sequence of events for the subject. Explain how you will prevent future occurrences.

Records for studies #1 and #2 listed above for which you were the sole principal investigator were found in disarray. It was difficult for the FDA investigator to locate and identify source data for study #2 listed above. Reasons for screening failures were not documented in subject files. Please explain how you intend to correct these conditions.

There are patterns at your site that indicate some subjects were entered into studies while meeting ineligibility criteria, followed in some cases, by sponsor exceptions of the subjects. In addition, some subjects were randomized incorrectly. This demonstrates lack of control, lack of supervision, and lack of adequate training regarding delegated responsibilities to other study personnel. We remind you that entry and exclusion criteria are developed in clinical protocols to establish a population for study. Please explain how these circumstances will be corrected for future studies you may conduct.

We remind you that you are responsible and may be held accountable for the conduct of your study coordinators and sub-investigators regarding the performance of clinical trials. Adequate training and supervision of your study personnel is essential to maintaining quality of data collection regarding the conduct of clinical trials.

Records submitted to the agency by the sponsor report that studies #1 and #2 listed above were terminated at your site by the sponsor on July 21, 1997. Your institution reported voluntary withdrawal from the studies in documents dated 7/23/97 to . We remind you that by signing the Form FDA 1572 you agree to maintain adequate and accurate records. "Adequate and accurate records" includes proper representation of study events reporting to the IRB(s) regarding changes in study activities.

The Form FDA 1572s dated 9/4/97 and 11/25/97 for study #5 listed above indicate that Dora Vazquez is a Registered Medical Assistant (RMA). The American Medical Technologists association and the American Association of Medical Assistants could not verify that Ms. Vazquez is a RMA. There is no record of Ms. Vazquez's certification. Also, Ms. Vazquez's Curriculum Vitae does not indicate that she has fulfilled the requirements of a RMA. Please explain.

We received the draft written standard operating procedures (SOPs) for
Please inform us of the expected time frames for completion of the SOPs. Please forward a copy of your completed SOPs regarding clinical trials to us. Your file will remain open until we receive a copy of your finalized version of the SOPs.

You are listed as principal investigator for 56 past and current clinical research studies. Continued non-compliance with the regulations governing the use of investigational drugs could affect not only the acceptability of the trial data but also the safety of human research subjects.

Deviations in the conduct of these studies suggest a lack of understanding of the procedures and requirements that govern the use of investigational new drugs. By signing the Statement of Investigator (Form FDA1572), you agreed to follow FDA regulations while conducting human clinical trials. The commitment includes ensuring that you will conduct the study in accordance with the protocol, that the requirements relating to obtaining informed consent and IRB review are met, and that adequate and accurate records of the study are maintained. Inspection results indicate that you did not follow the protocol, that one subject entered a study prior to protocol approval by the local IRB, and that you did not maintain complete and accurate records.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Failure to achieve prompt correction may result in enforcement action without further notice. These actions include clinical investigator disqualification proceedings which may result in an FDA determination that a clinical investigator is ineligible to receive investigational drugs.

Should you have any questions or comments about the contents of this letter or any aspects of clinical testing of investigational drugs, you may contact Debra Bower, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301)827-6221.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448, Attention: Steven A. Masiello, HFM-600.

Sincerely,

Steven A. Masiello
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics and Evaluation
and Research

Enclosures

FDA Form 483, Inspectional Observations
21 CFR Part 312
FDA Information Sheets for Institutional Review Boards and Clinical Investigators